

***Remarks***

Reconsideration of this Application is respectfully requested.

Claims 9-15 are pending in the application, with claim 9 being the independent claim.

Based on the following remarks, Applicants respectfully request that the Examiner reconsider all outstanding rejections and that they be withdrawn.

***I. Information Disclosure Statement***

Applicants note that a First Supplemental Information Disclosure Statement has been filed on July 18, 2007. Applicants respectfully request the Examiner initial and return a copy of Information Disclosure Statement Forms.

***II. Rejections under 35 U.S.C. § 103(a)***

The Examiner has maintained the rejection of claims 9-15 under 35 U.S.C. § 103(a) as being unpatentable over Isenring *et al.*, (U.S. Patent No. 6,407,100), Heinemann, *et al.* (U.S. Patent No. 6,103,717) and Jautelat *et al.* (U.S. Patent No. 5,789,430). Applicants respectfully traverse this rejection.

Applicants reiterate that for the reasons detailed in Applicants' Replies of May 1, 2006, October 26, 2006, and May 16, 2007, the Examiner has not established a *prima facie* case of obviousness against claims 9-15. In sum, the present invention is directed to a specific combination which possesses a synergistic effect and comprises trifloxystrobin, prothioconazole and fluoxastrobin. There is nothing in any of the cited patents (including the general statement that active compounds can be combined synergistically), the knowledge in the art, and the nature of the problem to be solved, that

would provide a reason for making the specific three-compound combination of trifloxystrobin, prothioconazole and fluoxastrobin.

**III. Synergistic Effects**

**a. "Synergistically effective" in Claims**

The Examiner stated that "[t]he synergism as presented in the specification is not in claims." Office Action, p. 7, under "Data in Specification."

Applicants reiterate that for the reasons detailed in Applicants' Reply of May 16, 2007, all pending claims 9-15 recite "synergistically effective" and request that the rejection be withdrawn.

In Reply to the Final Office Action dated July 26, 2006, Applicants submitted a Reply on October 26, 2006, in which independent claim 9 was amended adding "synergistically effective." Claims 10-15 depend from claim 9 and thus also include the "synergistically effective" limitation.

In Request for Continued Examination (RCE) Transmittal dated January 26, 2007, Applicants requested any previously filed unentered amendments and amendment enclosed with the RCE to be entered.

In the Office Action dated February 23, 2007, the Examiner acknowledged that Applicants' submission filed on January 26, 2007 has been entered. Office Action, p. 3, under "Continuation Examination under 37 CFR 1.114". Therefore, Applicants submit that all pending claims 9-15 recite "synergistically effective" and request that the rejection be withdrawn.

**b. Synergistic Effects**

The Examiner stated:

The Examiner has considered data presented in specification on page 11 in view of the remarks filed by Applicants. The application of the compounds (I), (II) and (III) are 100 g/ha and efficacy is 56, 56 and 67 percent respectively. It is unclear how this data relates to mixture where 25, 50 and 25 are g/ha and 78 percent is efficacy. Furthermore, how the number calculated is 78 when the ratio is 1:2:1. Applicants is requested to explain in detail . . . how this data represents a synergism.

Office Action, p. 7, under "Data in Specification" (underline original).

(i) ***Mathematical Calculation of Synergism***

(1) ***Applicants' Calculation***

First, Applicants wish to point out that the efficacy of 78% is not a calculated number. It is the actual efficacy data obtained from a test where the young barley plants were infested with *Pyrenophora teres*, a type of fungus. Then, the infested barley plants were treated with trifloxystrobin, prothioconazole or fluoxastrobin individually or treated with a combination of trifloxystrobin, prothioconazole and fluoxastrobin to test the curative effect of said individual fungicides and said combination of fungicides. See pages 10 and 11 of the specification.

The data at page 11 in the specification shows that when the infested barley plants were treated with trifloxystrobin, prothioconazole or fluoxastrobin *individually* at an application rate of 100 g/ha, trifloxystrobin, prothioconazole and fluoxastrobin has a percent efficacy of 56%, 56% and 67%, respectively. When the infested barley plants were treated with *a combination* of trifloxystrobin, prothioconazole and fluoxastrobin at an application rate of 100 g/ha (containing trifloxystrobin 25 g/ha, prothioconazole 50 g/ha and fluoxastrobin 25 g/ha), the combination has a percent efficacy of 78%.

For the reasons detailed in Applicants' Supplemental Reply of January 26, 2007, at an application rate of 25 g/ha in a 100 g/ha combination, trifloxystrobin has an expected percent efficacy of 14%<sup>1</sup>; at an application rate of 50 g/ha in a 100 g/ha combination, prothioconazole has an expected percent efficacy of 28%<sup>2</sup>; and at an application rate of 25 g/ha in a 100 g/ha combination, fluoxastrobin has an expected percent efficacy of 17%<sup>3</sup>. Thus, the sum of expected percent efficacy of the 100 g/ha combination is 59% (14%+28%+17%=59%). However, the data at page 11 in the specification shows that this combination has an observed efficacy of 78%, much higher than the expected efficacy of 59%. Therefore, the combination of trifloxystrobin, prothioconazole and fluoxastrobin as claimed in claims 9-15 has a synergistic effect.

**(2) The Examiner's Calculation**

According to the Examiner, "when calculating what is expected 56+56+67 should be divided by three." "Since the ratio of components used in present invention is 1:2:1. When component II is doubled than [sic] the total will be 56+(2x56)+67. This number divided by 3 gives 78 and divided by 4 gives about 58 for expected results. There is no synergism." Office Action, p. 7, under "Response to Remarks."

The Examiner acknowledged that if the ratio of components (trifloxystrobin:prothioconazole:fluoxastrobin) used in present invention is 1:1:1, the expected efficacy of the combination will be the total efficacy (56+56+67) divided by 3, or 60%. Likewise, if the ratio of components used in present invention is 1:2:1, since

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<sup>1</sup> (25/100) x 56% = 14%

<sup>2</sup> (50/100) x 56% = 28%

<sup>3</sup> (25/100) x 67% = 17%

component II is doubled, the expected efficacy will be  $56+(2 \times 56)+67$  divided by 4 because component II is counted twice for total efficacy calculation.

Thus, following the Examiner's calculation method, the expected efficacy of the three-component combination of trifloxystrobin, prothioconazole and fluoxastrobin at weight ratio of 1:2:1 is:

$$[56+(2 \times 56)+67]/4 = 58\%$$

As shown in Table 1 on page 11 of the specification, the combination of trifloxystrobin, prothioconazole and fluoxastrobin at weight ratio of 1:2:1 has an observed efficacy of 78%, much higher than the expected efficacy of 58%. Therefore, the combination of trifloxystrobin, prothioconazole and fluoxastrobin as claimed in claims 9-15 has a synergistic effect according to the Examiner's calculation method.

**(ii) *Alternative Showing of Synergism***

Alternatively, and in addition to the mathematical calculation of synergistic effect presented above, the synergistic effect of the present invention can be explained as follows:

1. The data at page 11 in the specification shows that when acting individually at an application rate of 100 g/ha, each individual compound, trifloxystrobin, prothioconazole and fluoxastrobin has a percent efficacy of 56%, 56% and 67%, respectively. Therefore, fluoxastrobin, with an efficacy of 67%, is the most potent fungicide in the combination.

2. While keeping the same application rate of 100 g/ha, but substituting 75 g of the most potent fluoxastrobin (efficacy of 67%) with a less potent fungicide [25 g of trifloxystrobin (efficacy of 56%) and 50 g of prothioconazole (efficacy of 56%)]. The

resulting three-component combination would be expected to be less potent than fluoxastrobin. In fact, the resulting three-component combination has a percent efficacy of 78%, much greater than that of even the most potent fungicide fluoxastrobin (67%) used alone at 100 g/ha. The improved efficacy can only be the result of a synergistic effect between the three components because in the absence of a synergistic effect, the resulting three-component combination would be expected to have a percent efficacy less than that of fluoxastrobin (67%) used alone. Therefore, the combination of trifloxystrobin, prothioconazole and fluoxastrobin as claimed in claims 9-15 has a synergistic effect.

**(iii) Colby Formula**

The Examiner questioned the validity of the Colby formula, citing *Ex parte Quadranti*. Office Action, p. 6, under "Claim Rejections-35 USC § 103." Applicants discussed the Colby formula in the specification to illustrate one method of calculating an expected efficacy of a given three-component combination. However, as shown above, Applicants do not rely solely on the Colby formula to determine an expected efficacy of three-component combination of trifloxystrobin, prothioconazole and fluoxastrobin. Thus, a showing of synergism does not depend on the validity of Colby formula alone.

**(iv) Additional Evidence of Synergism**

The data at page 11 in the specification shows the synergistic fungicidal effect of the three-component combination of trifloxystrobin, prothioconazole and fluoxastrobin at the weight ratio of 1:2:1 against *Pyrenophora teres* on barley plants. Additional efficacy data of trifloxystrobin, prothioconazole and fluoxastrobin combination at a different

weight ratio, against different types of fungus, and on a different crop/plant (wheat) is provided in the accompanying Declaration by Dr. Peter Dahmen under 37 C.F.R. § 1.132 submitted herewith.

**(1) *Blumeria graminis* preventive test**

The study described in Table 1 in Dr. Dahmen's Declaration shows the fungicidal effect of a combination of trifloxystrobin, prothioconazole and fluoxastrobin at the weight ratio of 1:1:2. *Blumeria graminis* fungus on wheat was tested. In this study, the wheat plants were treated with trifloxystrobin, prothioconazole, fluoxastrobin or a combination of trifloxystrobin, prothioconazole and fluoxastrobin. Then, *Blumeria graminis* fungus was introduced to the treated wheat plants to test the preventative (protective) effect of the fungicides individually or in a combination. As shown in Table 1 of Dr. Dahmen's Declaration, when acting individually at an application rate of 12.5 ppm (parts per million) trifloxystrobin, 12.5 ppm prothioconazole or 25 ppm fluoxastrobin, each fungicide has a percent efficacy of 25%, 38% and 0%, respectively. When 12.5 ppm trifloxystrobin is combined with 12.5 ppm prothioconazole and 25 ppm fluoxastrobin and acting together, the combination has a percent efficacy of 88%.

According to Colby formula, the calculated percent efficacy of the combination is 53%. However, the observed percent efficacy is 88%, much greater than the calculated percent efficacy. Thus, the combination of trifloxystrobin, prothioconazole and fluoxastrobin at the weight ratio of 1:1:2 has a synergistic protective effect against *Blumeria graminis* fungus on wheat.

Alternatively, and in addition to the Colby formula, the synergistic protective effect of the combination can be explained as follows:

In the absence of a synergistic effect, the combination of trifloxystrobin, prothioconazole and fluoxastrobin would be expected to have an additive efficacy of 63% ( $25\%+38\%+0\%=63\%$ ). Because the actually observed efficacy of the combination of is 88%, much higher than the additive efficacy of 63%, the combination has a synergistic effect.

**(2) *Blumeria graminis* curative test**

The study described in Table 2 in Dr. Dahmen's Declaration shows the fungicidal effect of a combination of trifloxystrobin, prothioconazole and fluoxastrobin at the weight ratio of 1:2:1. *Blumeria graminis* fungus on wheat was tested. In this study, the wheat plants were infested with *Blumeria graminis* fungus. Then, the infested wheat plants were treated with trifloxystrobin, prothioconazole, fluoxastrobin or a combination of trifloxystrobin, prothioconazole and fluoxastrobin to test the curative effect of the fungicides individually or in a combination. As shown in Table 2, when acting individually at an application rate of 50 ppm trifloxystrobin, 100 ppm prothioconazole or 50 ppm fluoxastrobin, each fungicide has a percent efficacy of 75%, 88% and 38%, respectively. When 50 ppm trifloxystrobin is combined with 100 ppm prothioconazole and 50 ppm fluoxastrobin and acting together, the combination has a percent efficacy of 100%.

According to Colby formula, the calculated percent efficacy of the combination is 98%. However, the observed percent efficacy is 100%, exceeding the calculated percent efficacy. Thus, the combination of trifloxystrobin, prothioconazole and fluoxastrobin at the weight ratio of 1:2:1 has a synergistic curative effect against *Blumeria graminis* fungus on wheat.



**(3) *Leptosphaeria nodorum* preventive test**

The study described in Table 3 in Dr. Dahmen's Declaration shows the fungicidal effect of a combination of trifloxystrobin, prothioconazole and fluoxastrobin at the weight ratio of 1:1:2. *Leptosphaeria nodorum* fungus on wheat was tested. In this study, the wheat plants were treated with trifloxystrobin, prothioconazole, fluoxastrobin or a combination of trifloxystrobin, prothioconazole and fluoxastrobin. Then, *Leptosphaeria nodorum* fungus was introduced to the treated wheat plants to test the preventative (protective) effect of the fungicides individually or in a combination. As shown in Table 3, when acting individually at an application rate of 50 ppm trifloxystrobin, 50 ppm prothioconazole or 100 ppm fluoxastrobin, each fungicide has a percent efficacy of 29%, 0% and 0%, respectively. When 50 ppm trifloxystrobin is combined with 50 ppm prothioconazole and 100 ppm fluoxastrobin and acting together, the combination has a percent efficacy of 86%.

According to Colby formula, the calculated percent efficacy of the combination is 29%. However, the observed percent efficacy is 86%, much greater than the calculated percent efficacy. Thus, the combination of trifloxystrobin, prothioconazole and fluoxastrobin at the weight ratio of 1:1:2. has a synergistic protective effect against *Leptosphaeria nodorum* fungus on wheat.

Alternatively, and in addition to the Colby formula, the synergistic protective effect of the combination can be explained as follows:

In the absence of a synergistic effect, the combination of trifloxystrobin, prothioconazole and fluoxastrobin would be expected to have an additive efficacy of 29% ( $29\%+0\%+0\%=29\%$ ). Because the actually observed efficacy of the combination

of trifloxystrobin, prothioconazole and fluoxastrobin is 86%, much higher than the additive efficacy of 29%, the combination has a synergistic effect.

In summary, additional testing of the fungicidal effect of claimed combination at a different weight ratio, against different types of fungus on wheat provides further evidence that the claimed combination has synergistic effect in controlling fungi on crops or plants. Therefore, Applicants respectfully submit that the data supports the conclusion that the claimed combination has a synergistic effect in controlling fungi.

***Conclusion***

All of the stated grounds of objection and rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider all presently outstanding objections and rejections and that they be withdrawn. Applicants believe that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration of this Amendment and Reply is respectfully requested.

Respectfully submitted,

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